

### **REMARKS**

Claims 12-14, 16, 23-25, 27-29, 31, 32-34 are pending in the subject application. Claims 12, 23, 27 and 32 have been amended. No new matter is raised by these claims amendments.

#### **Double Patenting**

The Examiner provisionally rejects claims 12-14, 16, 23-25, 27-29, 31, and 32-34 under the judicially-created doctrine of obvious-type double patenting over co-pending application 09/842,111 in view of Gonzalez et al. (U.S. 6,015,673). Applicants respectfully submit that the present claims are not obvious in light of Gonzalez, as demonstrated below. However, if the Examiner still maintains the obvious-type double patenting rejection over co-pending application 09/842,111, Applicant will file a terminal disclaimer pursuant to 37 C.F.R. §§1.130(b) and 1.312, upon a showing by the Examiner that the claims at issue are in condition for allowance, and if the 09/842,111 claims have issued.

#### **Rejection under 35 U.S.C. § 103(a)**

Claims 12-13, 16, 23, 24, 27, 28, 31, 32 and 34 have been rejected under 35 U.S.C. §103 (a) over Gonzalez et al. (U.S. Patent 6,015,673) in view of Willhauck et al. (Biotechniques (1998) 25:656-659) and further in view of Buck et al. (Biotechniques (1999) 27 (3): 528-536) and further in view of Stanta et al. (Biotechniques (1991) 11(3): 303, 306, and 308).

Applicants respectfully disagree as Gonzalez does not teach each and every element of the claimed invention and Willhauck, Buck and Stanta do not make up for these deficiencies. The fact that Gonzalez teaches a method of freezing or fixing a sample for detection is irrelevant, as the present claims involve fixing a portion of a tumor sample in paraffin. Gonzalez does not teach or suggest this. The present claims involve isolating mRNA from the fixed and paraffin embedded (FPE) tumor tissue.

Gonzalez does not teach or suggest this. The present claims involve amplifying mRNA from the FPE tumor tissue. Gonzalez does not teach or suggest this. The present claims also involve comparing expression levels of DPD in the amplified mRNA from the FPE tumor sample with the mRNA from an internal control gene. Gonzalez does not teach or suggest this. The present claims also involve the use of claimed primers for amplifying the mRNA. Gonzalez does not teach the claimed primers, regardless of the homology of those primers identified in Gonzalez. Willhauck does not teach or suggest these missing elements and does not make up for the shortcomings of Gonzalez. For example, the Examiner cites Willhauck for teaching comparing the amount of the target gene to an internal gene, including B-actin. Willhauck, however, actually teaches away from the use of housekeeping genes, such as GAPDH and B-actin. (See page 656 column 1). Specifically, Willhauck states that such housekeeping genes are “not suitable for reliable detection of tumor targets with low mRNA expression levels.” Thus, applicants respectfully assert that the combination of Gonzalez and Willhauck does not teach nor suggest the claimed invention and therefore does not render the claims obvious.

Furthermore, in response to the Examiner’s assertion that one would have a reasonable expectation of success in using the primers of Gonzalez based on the teaching of Buck, as addressed above, the applicants respectfully disagree. Applicants argue that rather than Buck teaching that there is a presumption that “all primers selected according to the ordinary criteria” would be expected to function, Buck teaches away from this presumption. In particular, Buck states that it is only with optimal sequencing conditions with highly pure template and primer would you expect the results presented in the article (see page 535, column 2, which notes that the plasmid template was purified by double banding in CSCI-ethidium bromide isopycnic density gradients). Thus, in the absence of these factors, one skilled in the art would not be guaranteed a reasonable expectation of success. Therefore, applicants respectfully assert that the combination of Gonzalez and Buck does not teach nor suggest the claimed invention and therefore does not render the claims obvious. Accordingly, applicants

respectfully request withdrawal of this ground of rejection.

In response to the Examiner's assertion that it would be obvious to one skilled in the art to combine the teaching of Gonzalez with Willhauck, Buck and Stanta, as addressed above, the applicants respectfully disagree. Applicants argue that as with Willhauck, Stanta actually teaches away from the claimed invention and, thus, one would not be motivated to combine the teachings of Gonzalez with the teachings of Stanta to arrive at the presently claimed invention. For example, the Examiner cites Stanta for teaching a chaotropic agent, yet Stanta, on page 307 column 1, characterizes the second step of the method as teaching "a proteolysis step with a high concentration of proteinase K in the presence of 1 M guanidinium thiocyanate" to allow for efficient RNA extraction without further degradation. In contrast, the claimed method uses a chaotropic agent (without a high concentration of proteinase K) at higher temperatures for shorter times to extract mRNA from fixed paraffin embedded samples. Additionally, in light of the present amendments, the allegation that 45° C was "about 50 to about 120 °C" or "about 75 to about 120 °C" is now moot. Thus, applicants respectfully assert that the combination of Gonzalez and Stanta does not teach nor suggest the claimed invention and therefore does not render the claims obvious. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

Claims 14, 25, 29 and 33 have been rejected under 35 U.S.C. §103 (a) over Gonzalez et al. (U.S. Patent 6,015,673) in view of Willhauck et al. (Biotechniques (1998) 25:656-659), further in view of Buck et al. (Biotechniques (1999) 27 (3): 528-536), further in view of Stanta et al. (Biotechniques (1991) 11(3): 303, 306, and 308) and further in view of Johnston, et al. (Cancer Research, 55 (7): 1407-12 (April 1995)).

As previously stated, Applicants respectfully disagree as Gonzalez does not teach each and every element of the claimed invention and Willhauck, Buck, Stanta and Johnston do not make up for

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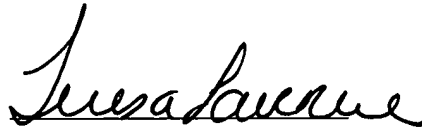
these deficiencies. As noted above, Willhauck actually teaches away from the use of housekeeping genes, such as GAPDH and B-actin. Thus, applicants respectfully assert that one skilled in the art would not be motivated to combine Gonzalez and Johnston, in view of Willhauck, and therefore, this combination does not teach nor suggest the claimed invention and therefore does not render the claims obvious. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

### CONCLUSION

It is believed that the present claims are in conditions for allowance and earnestly request allowance. Extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 11-0600. The Examiner is invited to contact the undersigned attorney if necessary to expedite allowance.

Respectfully submitted,

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